UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/981,087	05/27/98	ELMORE M	1581.0200000

HM22/0316

NIXON & VANDERHYE P.C
1100 NORTH GLEBE ROAD, 8TH FL.
ARLINGTON VA 22201-4714

EXAMINER	
TURNER, S	
ART UNIT	**PAPER NUMBER**
1644	14

DATE MAILED: 03/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/981,087	Elmore et al
Examiner	**Group Art Unit**
Sharon L. Turner, Ph.D.	1644

☒ Responsive to communication(s) filed on *1-7-00*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-25* is/are pending in the applicat

Of the above, claim(s) *13-18 and 25* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-12 and 19-24* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-25* are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Response to Amendment

1. The Examiner of U.S. Patent application SN 08/981,087 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1644.

2. The certified copy of the GBR 9511909.5 Priority Document, Alternate Rule 181 Petition and Amendment filed 1-7-00 have been entered into the record. The Priority Document and Amendment have been fully considered by the examiner. The Petition will be forwarded to the Commissioners Office for proper consideration.

3. Claims 1-25 are pending.

4. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

Rejections Maintained

5. In regard to the traversal of the restriction requirement, applicants arguments direct the examiners attention to MPEP 1893.03 and Appendix AI, Annex B Part 2, Example 17. Applicants propose that the invention of Group I, the polypeptide, shares unity with the DNA of Group II encoding the polypeptide of Group I.

Applicants request for reconsideration and withdrawl of the restriction requirement based on these arguments has been considered but is not deemed persuasive. As set forth in the restriction requirement dated 6/16/99, the two groups of claims do not relate to a single general

inventive concept under PCT Rule 13.1 since, under PCT Rule 13.2, they lack the same or corresponding special technical feature which is the polypeptide.

As set forth previously, the expression "special technical feature" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes *over the prior art*. Further, as set forth in the restriction requirement, instant claims all involve the polypeptide free of botulinum toxin activity and free of toxoid which induces protective immunity to type F botulinum toxin. It is clear from East et al (Current Microbiology 29:69-77, 1994) that said polypeptide does not define a contribution over the prior art. East et al disclose the nucleic acid and amino acid sequence of a gene encoding for a nontoxic polypeptide component of botulinum type F (distinct from botulinum neurotoxin or BoNT). Thus, East teaches the special technical feature of the invention, a polypeptide free of botulinum toxin activity and free of toxoid, see in particular Figure 4 for complete sequence information of the non-toxic-nonhemagglutinin (NTNH) component of the botulinum toxin complex encoded by nonproteolytic *C. botulinum* type F. Since the special technical feature does not define a contribution over the prior art, and no other link between the inventions of Group I and Group II exists, then as set forth in the MPEP, Annex B, Part I, p. AI-36, column 2, lines 6-14, in particular, unity of invention is lacking and an objection of lack of unity *a posteriori* may be raised. Thus, for these reasons and as set forth in Papers 8 and 10, mailed 6/16/99 and 10/7/99, respectively, the restriction requirement is still deemed proper and is therefore made FINAL.

6. Claims 13-18 and 25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

7. This application contains claims 13-18 and 25 drawn to an invention nonelected with traverse in Paper Nos. 7, 12 and 13. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 7 and 9-10 stand rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Said claims are drawn to "a polypeptide" and polypeptide composition comprising " a polypeptide" which reads on naturally occurring polypeptides as claimed, i.e. polypeptides that are not altered by the hand of man.

Applicant submits that the amendments to claims 1-7 and 9-10 obviate the rejection.

Contrary to applicants assertion, claims 7, and 9-10 remain drawn to a (nonisolated) polypeptide, see in particular 7(2) which has not been amended consistent with claims 1-6 and claims 9-10 as they depend from claim 7.

New Rejections

Priority

9. Applicants have perfected their claim of priority based upon GBR 9511909.5 for fusion proteins. Thus, the priority date awarded instant claims 1-6, 12 and 19-21 is 6/12/95. Claims 7, 9 and dependent claims thereof lack support for 2 peptide compositions. Claims 22-24 lack enablement commensurate in scope with the claims as set forth below.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 7, 9 and dependent claims thereof (claims 8 and 10-11) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 7 and 9 recite compositions comprising 2 separate proteins which provide protective immunity against botulinum toxin and which facilitate or enhance purification and that bind a chromatography column. However instant specification does not disclose any 2 peptide component composition which provides these properties. Instant specification only shows such properties with a fusion protein. Absent

further guidance one of skill in the art could not make and use the claimed invention without further undue experimentation.

12. Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increased survival against challenge with C. botulinum Langland BoNT/F by immunization with MBP-BoNT/$F_{848-1278}$ fusion protein, does not reasonably provide enablement for claims 22-24 as claimed in particular with respect to any protein which is free of botulinum activity, free of toxoid and with respect to protection against type F botulinum toxin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition. The skilled artisan also recognizes that immunological responses depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Instant specification discloses an example of a fusion protein vaccine MBP-BoNT/$F_{848-1278}$ which provides increased survival upon challenged with C. botulinum Langland BoNT/F. However, the

claims recite vaccine compositions and methods of vaccinating which encompass proteins other than MBP-BoNT/$F_{848-1278}$ and which protect against botulinum type F toxins. Protection indicates that vaccinated animals are resistant to infection, yet instant specification does not disclose whether or not surviving animals are resistant to infection. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives and fragments encompassed for vaccination, and the requirement that the vaccine be protective against botulinum type F toxins one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

The specification does not enable the broad scope of the claims which encompass a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke immune responses which would be protective to any particular botulinum toxin. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful other than MBP-BoNT/$F_{848-1278}$. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the cliamed derivatives in a manner reasonably correlated with the scope of the claims broadly including any number of deletions, additions and/or substitutions of any size with protective capabilities. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in

the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 8, 10 and 11 recite limitations with respect to a single polypeptide. However, claims 7 and 9 recite two separate peptides. The structure of the proteins of claims 7 and 9 do not support or provide antecedent basis for a third peptide which depends therefrom but does not share common structure, i.e., the two separate proteins when joined constitute a third disclosed peptide which is not common to either of the two separate proteins as claimed in claims 7 and 9. Thus, there is insufficient antecedent basis for the limitations in claims 8, 10 and 11.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. Claim 1-2, 12 and 22 stand rejected under 35 U.S.C. 102(a) as set forth in Paper No. 10, mailed 10/7/99 and as further reiterated herein, as being anticipated by Sesardic et al (PCT Publication No. WO 94/21684, publication date 9/29/94).

Applicants assert that the teaching of Sesardic is to utilize a polypeptide, which may be a region of a botulinum toxin, as an enhancer for the known type of toxoid vaccines. The vaccines mentioned are the conventional ones such as the pentavalent A-E toxoid (see, for example claim 17). Applicants therefore conclude that Sesardic does not teach the invention of the present claims, in particular applicants assert that there is no teaching in Sesardic of polypeptides for protection against specific types of botulinum toxin, namely type F.

Applicants arguments have been considered but are not persuasive. First, applicant seems to imply that instant claims are directed to a method of protection by administration of polypeptides which provide protection against type F botulinum toxin. However, the examiner points out that the claims are not so limited. Instant claims are directed to a polypeptide which is free of botulinum toxin activity and which is free of toxoid which induces protective immunity to a type F botulinum toxin, see p. 3, lines 5-16 and 6, lines 12-13, and Table I, in particular. The polypeptides of Sesardic are both free of botulinum toxin activity and free of toxoid. Claim 2 further provides that the polypeptide is *capable* of eliciting, in a mammal, an immunological response that is protective against type F botulinum toxin. Thus, this limitation is not a requirement of the polypeptides as claimed since the peptides merely need be capable of eliciting an immunological response. Nevertheless, Sesardic teaches that sera from mice pre primed with

the polypeptides of the invention, i.e., P1, had a 10 fold higher level of antitoxin antibody response as exemplified in Table 5 and also that cross reactive T cell responses induced by P1 to Botulinum toxoid type F, suggests that immunising with P1 is of potential use in augmenting the anti-botulinum toxin B, C and F responses, see pp. 18-20 and Table 6 in particular. Thus, Sesardic not only teaches that P1 is capable of eliciting immunological responses but also teaches that P1 does elicit immunologicalt responses (T-cell priming and induction of antibody). Claim 12 provides for the polypeptide and a pharmaceutically acceptable carrier as is taught by Sesardic at p. 21, lines 9-14, in particular. Claim 22 provides a method of vaccinating a mammal against a botulinum toxin comprising the administration of the vaccine of claim 12. Sesardic teaches methods of vaccinating mammals against botulinum toxin for example by administration of P1 with botulinum toxoids or the pentavalent vaccine, see also p. 3-7. Thus, the reference teachings of Sesardic anticipate instant claims.

17. Claims 3-4, 7-10, and 19-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Sesardic et al (PCT Publication No. WO 94/21684, publication date 9/29/94) as evidenced by Sigma Catalog 1992.

Claim 3 is drawn to a isolated polypeptide according to claim 2 comprising a fragment or a derivative of a heavy chain of a type F botulinum neurotoxin. The Sesardic peptide P1 shares single amino acid residues with a heavy chain of a type F botulinum neurotoxin and thus P1 anticipates claim 3, see Table 1, p. 12, in particular. P1 is less than 600 amino acids long and thus anticipates claim 4, see Table 1, p. 12, in particular. Claim 7 is anticipated as set forth

above, Sesardic teaches a two peptide vaccine composition comprising the P1 peptide and F Btxd. The polypeptides are free of toxin activity and capable of inducing protective immunity against botulinum toxin (Btxd B, C or F polypeptides). The peptides facilitate or enhance purification of the composition via immunoreactivity from animal sera, see for example Table 6 and as a nonspecific peptide blocker on glassware (as BSA). The examiner further notes that any known peptide meets the limitations of (2) since the knowledge of any peptide sequence or reactivity aids in the isolation of that compound. Claim 8 is anticipated as taught P1 shares single amino acid residues in a fusion protein i.e., a longer polypeptide chain of 27 residues, see Table 1. These residues will bind chromatography/affinity chromatography columns, as evidenced by Sigma Catalog, 1992, p. 1585 and 1592-93, and thus claims 9-10 are anticipated. As set forth, Sedaric teaches pharmaceutical compositions and a method of vaccinating a mammal with the polypeptide(s) of instant claims and thus, as set forth Sedaric anticipates claims 19-24. For these reasons Sedarics teachings anticpate the claimed invention.

18. Claims 1-4, 7-12 and 19-24 rejected under 35 U.S.C. 102(b) as being anticipated by Simon et al, US Patent No. 5,178,859, issued Jan. 12, 1993. Simon et al teach claim 1, a protein vaccine against lyme disease which is free of botulinum toxin activity and free of toxoid which induces protective immunity to a type F botulinum toxin, see abstract in particular. Simon et al teach claim 2 because the polypeptide is free of botulinum toxin activity, is free of toxoid and is *capable* of eliciting, in a mammal an immunological response, that is protective against type F bothulinum toxin, see column 4 lines 34-45, Example 4 and Example 5, in particular. The

Simon reference is silent as to whether the response is protective against type F botulinum toxin. However, because the polypeptide meets the structural limitations of the claim and is capable of eliciting, in a mammal an immunological response, absent evidence to the contrary, the polypeptide composition of Simon et al is capable of eliciting antibodies which are protective against type F botulinum toxin. Claim 3 is anticipated, the polypeptide of Simon et al shares a fragment or a derivative of a heavy chain of a type F botulinum neurotoxin, see in particular Figure 1, shared single amino acid residues, for example lysine. Claim 4 is anticipate since the single amino acid residues are up to 600 amino acids in length, see Figure 1. Claims 7 is anticipated by the polypeptide(s) of Simon et al, see for example column 7, lines 1-3. Claim 8 and claim 11 as it depends therefrom are anticipated by the fusion proteins sharing the characteristics of claim 7, see for example column 8, line 63-column 9, line 24. Simon anticipates claims 9-10, see column 10, lines 17-41, recombinant proteins isolated by affinity chromatography using LA-2 monoclonal antibodies covalently bound to activated Sepharose CL 4B. Simon anticipates claim 12 and 19-24, pharmaceutical compositions and methods of vaccinating, see column 3, lines 30-39, column 13, lines 44-53 and Table 4. Thus, as the polypeptides, fusion proteins, fragments, and derivatives whcih are capable of binding via affinity chromatography via antibodies (such as LA-2), pharmaceutical compositions and methods of vaccinating are anticipated by Simon et al, the reference teachings anticipate the claimed invention.

Status of Claims

19. No claim is allowed.

20. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973.

Sharon L. Turner, Ph.D.
March 15, 2000

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER